

REMARKS

Claims 1 to 103 are pending in the present application. Claims 58 to 60 were rejected in the Office Action dated February 7, 2007. Claims 1 to 57 and 61 to 99 have been withdrawn from consideration.

Claim 58 has been amended and claim 100 is added by the present amendment. Support for those claims is found throughout the specification, for example, at the Abstract, pages 4-5 and 11, and in original claims 1-2 and 58-60.

Claim 58 has been amended to more clearly indicate that the invention is directed to a method of screening for cocrystals.

The Claims Are Not Indefinite

The Office Action rejected claims 58-60 under 35 U.S.C. §112, second paragraph, as indefinite. More particularly, the Office Action stated that the term “coordinate more strongly” was a relative term that rendered the claims indefinite, and that it is not clear to one of ordinary skill in the art what the term “active agent” and “guest” encompass.

“The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available.” Section 2173.02, Manual of patent Examining Procedure (MPEP). “Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.” *Id.*

The Office Action asserts that the specification does not provide one of ordinary skill in the art with a method of determining the relative strengths of coordination of the guest with the counterion or of the strength of coordination within a crystal. Applicant submits that the Office

Action has overlooked the extensive teachings regarding the relative strength of coordination provided by the present application. See, for example, page 6-9 of the present application. Among the relevant teachings as to determining the relative strength of coordination in forming cocrystals, the present application states:

It is useful in forming cocrystals to recognize that relatively weak interactions may be replaced by stronger interactions, even though those stronger interactions may be relatively weak themselves, compared to other interactions. For example, an undercoordinated chloride may have one strong hydrogen bond donor and several weak hydrogen bond donors or two strong hydrogen bond donors and several weak hydrogen bond donors. In a cocrystal, weaker interactions may be replaced by stronger interactions, although those stronger interactions may still be weaker than the strong interactions (charge-assisted hydrogen bonds) present in fluoxetine HCl crystals. The strongest interactions involving chloride ions in crystal structures of organic salts are the charge assisted hydrogen bonds that invariably form between the protonated nitrogen base and the chloride ion. The strongest interactions between neutral molecular groups and the chloride ion involve acids and the chloride ion. Carboxylic acids, for instance, have strong interactions with chloride ions. It can be seen that a combination of carboxylic acids and hydrochloride salts of nitrogen containing bases are especially well suited to cocrystal formation (as demonstrated by the examples included).

(pages 7-8).

Additional guidance as to evaluating undercoordination may be found in the inventor's prior work (which is incorporated by reference herein in its entirety), particularly in its discussion of nonbonded motifs: Scott L. Childs, "Nonbonded Interactions In Molecular Crystal Structures", Emory Univ., USA, available from UMI, Order No. DA3009424 (288 pp.), Dissertation Abstract Int. Ref. B2001, 62(3), 1394. In some circumstances, the undercoordination can be determined by measuring distances, comparing profiles in the Cambridge Structural Database, measuring the pKa of the donors and acceptors, or evaluating the ratio of strong hydrogen bond donors to available acceptors. Other crystal engineering theories may also be used.

(page 9). A person of ordinary skill in the art would understand what is meant by theorizing coordination of the counterion by hydrogen bond interactions within the crystal, and selecting a guest to coordinate more strongly with the counterion than the coordination within the crystal.

Applicant respectfully submits that the Office Action is in error with respect to the terms "active agent" and "guest". A person of ordinary skill would readily understand the meanings of

those terms as used in the specification. This is not a case where no direction or discussion is provided about claim terms – to the contrary, the specification includes an extensive discussion regarding active agents and guests and provides examples of each. (See, for example, pages 14-25).

The Office Action asserts that a chemical structure must be provided which specifies which structures are included and excluded from the terms “active agent” and “guest”. This is incorrect, since there is no requirement that a claim term must be limited to a chemical structure. “There is nothing inherently wrong with defining some part of an invention in functional terms.” MPEP §2173.05(g).

Applicant respectfully submits that claims 58-60 not indefinite. Applicant requests reconsideration of this ground of rejection.

The Claims Comply With the Written Description Requirement

The Office Action rejected claims 58-60 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement with regard to the terms “active agent” and “guest”. More particularly, the Office Action stated that claims 58-60 do not contain a complete generic formula for either of those terms.

Applicant submits that this rejection is erroneous. First, it should be noted that claims 58-60 are original claims; the Office Action is not raising a written description issue as to new claims or amended claims. Original claims are entitled to a strong presumption that they comply with the written description requirement. “There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed.” MPEP § 2163.

Furthermore, the present application clearly conveys that the inventor had possession of the claimed subject matter. A person of ordinary skill would have no doubt that the inventor had

possession of a method of preparing a cocrystal of a salt of an active agent and a guest, and he/she would not believe that the invention was limited to working examples. A person of ordinary skill would know what an “active agent” is, especially since the specification explicitly discusses this term.

The active agent is the molecule whose activity is desirable or the object of interest. It is contemplated that one or more active agents may be employed in a cocrystal, according to any of the present techniques. For example, where the active agent is an active pharmaceutical ingredient, the pharmaceutical activity of the active agent is desirable. Other active agents may be nutraceuticals, agricultural chemicals, pigments, dyes, explosives, polymer additives, lubricant additives, photographic chemicals, or structural and electronic materials.

(page 14). As for the term “guest”, the specification provides an extensive discussion (see pages 19-25) and hundreds of species of guests. For example, Table 2 sets forth a group of preferred guests that includes over **fourteen hundred of species**. As the Office Action must acknowledge, the disclosure of an adequate number of species is sufficient to provide written description of the genus. It is difficult to imagine a more extensive identification of species than that provided in the present application.

The Office Action relies heavily on the legal principles from *University of California v. Eli Lilly and Co.*, F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) to support its assertion that the present application does not provide an adequate written description. That case, which related to a patent that disclosed a sequence for rat insulin cDNA but had claims encompassing mammalian, vertebrate and human cDNA, has many factual distinctions from the present case. In particular, the present application does not relate to nucleotide sequences. Moreover, legal quotes are not adequate to carry the Office’s burden for a written description rejection.

The inquiry into whether the description requirement is met must be determined on a **case-by-case basis** and is a **question of fact**. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is **presumed to be adequate**, unless or until sufficient evidence or reasoning to the contrary has been

presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

MPEP §2163.04 (emphasis added).

Applicant respectfully submits that the Office Action has failed to carry its burden to establish that claims 58-60 are unpatentable for lack of written description. Applicant requests reconsideration of this ground of rejection.

The Claims Comply With the Enablement Requirement

The Office Action rejected claims 58-60 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. More particularly, the Office Action acknowledged that the specification enables methods of making several types of cocrystals but contended that the disclosure was not commensurate with the scope of the claims.

The Office Action relies on a 1994 article (Gavezzotti, *Acc. Chem. Res.* 1994, 27, 309-314) as showing that the formation of cocrystals is very unpredictable. Applicant submits that whereas the formation of cocrystals is unpredictable, claims 58-60 are directed to methods of screening for cocrystals. These screens rely on the chemical insight described elsewhere in the specification so as to increase the probability of preparing a cocrystal.

The formation of cocrystals is very unpredictable. It is difficult to foresee structural changes as a function of changes in molecular substitution patterns or in molecular geometry. However, **the present disclosure provides greater predictability and better probability of success in designing and forming cocrystals.**

(page 9 (emphasis added)). Note also, Applicant is not claiming in the screens the cocrystals prepared by the screens. Applicant cannot predict the stoichiometry or properties of resulting cocrystals. Applicant have succeeded, however, in developing methods for screening which greatly increase the likelihood that a cocrystal, whatever its stoichiometry or properties, will be successfully

prepared. Thus, the Office Action failed to recognize that the present specification provides teachings that improve the ability to predictably screen for cocrystals of a salt of an active agent and a guest.

As discussed above, the specification provides detailed teachings regarding the role of coordination of a counterion and a guest in formation of cocrystals and describes methods of preparing cocrystals in light of those teachings. (See pages 3-4 and 6- 9). The application provides working examples of methods of preparing several different cocrystals comprising salts of an active agent and guests. (Examples 1, 2 and 9). The specification discloses several active agents and hundreds of guests, and it contains a prophetic example (Example 7) employing each possible combination of the salts of active agents and guests identified earlier in the specification. As mentioned above, the specification identifies hundreds of guests for use in preparation of cocrystals. Applicant respectfully submits that the Office Action did not give adequate consideration to these teachings with regard to the issue of enablement.

Applicant submits that the Office Action has failed to show that claims 58-60 are unpatentable for lack of enablement. Applicant requests reconsideration of this ground of rejection.

The Claims Are Not Anticipated By US Patent No. 2,665,277

The Office Action rejected claims 58-60 under 35 U.S.C. §102, as being anticipated by Homeyer et al. US Patent No. 2,665,277. The Office Action stated that Homeyer et al. describe a method of making morphine phosphate hemihydrate, where the crystal contains a salt of an active agent (morphine phosphate) and a guest (water). With regard to the method steps recited in claim 58, the Office Action refused to give any patentable weight to the step of “theorizing coordination

of the counterion by hydrogen bond interactions within said crystal". The Office Action asserted that this step is purely mental with no physical consequences.

Applicant submits that the Office Action is in error, both factually and legally. The Office Action is factually wrong in stating that the "theorizing coordination" step has no physical consequences. In the claimed method, later steps can be based upon the "theorizing coordination" step. For example, in claim 58, after the "theorizing coordination" a guest is selected to coordinate more strongly with the counterion than the coordination within said crystal, and a solution, melt or physical mixture is prepared, which is a physical step. The Office Action is legally wrong, in that it cannot ignore a portion of a claim simply because the Office Action views it as "purely mental." All the elements of a claim must be considered in examination.

As for claim 100, Homeyer does not teach a cocrystal with a carboxylic acid having at least four carbon atoms. Thus, for this additional reason, Homeyer does not anticipate claim 100,


Homeyer et al. does not disclose the subject matter of claims 58-60. Homeyer et al. does not disclose a method of preparing a cocrystal of a salt of an active agent and a guest that includes the steps of theorizing coordination of the counterion by hydrogen bond interactions within the crystal, and selecting a guest to coordinate more strongly with the counterion than the coordination within the crystal.

Applicant respectfully submits that the Office Action has failed to show that claims 58-60 are anticipated by Homeyer et al. Applicant requests reconsideration of this ground of rejection.

Conclusion

Applicant requests allowance of claims 58 to 60 and 100. The Examiner is invited to telephone the undersigned to discuss any questions or be of any assistance to the Examiner in the reconsideration and allowance of this case.

Respectfully submitted,

A handwritten signature in dark ink, reading "Michael B. Harlin". The signature is fluid and cursive, with the first name "Michael" being the most prominent. The signature is written over a horizontal line.

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